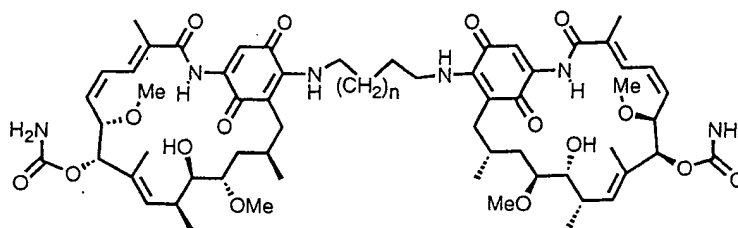


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Q²

associated with a poor prognosis. HER1 and HER2 are attractive targets for therapeutic development. Antibodies against each of these receptors have been shown to have antitumor effects in animal models. Fan, et al., *Curr Opin Oncol* 10, 67-73 (1998). Recently, an anti-HER2 antibody was shown to be effective in the treatment of breast cancers in which the HER2 protein is overexpressed. Ross et al., *supra*; Pegram, et al., *J Clin Oncol* 16, 2659-2671 (1998). However, therapeutic effects were seen in only a minority of patients and were usually short-lived. It is not known whether this is due to

Q³ ✓ Page 3, please replace the structure at lines 19-24 with the following structure:



Dimers: n = 1-9

Q⁴ ✓ Page 5, please replace the first partial paragraph and the first full paragraph with the following:

cause them to undergo homodimerization or heterodimerization with other members of the family. This activates the tyrosine kinase activity of the constituents of the dimer, causes their autophosphorylation and initiates transduction of the mitogenic signal. Although a direct interaction of hsp90 and HER-kinases has not been convincingly demonstrated, the fact that sensitivity of HER2 and other kinases to geldanamycin requires the catalytic domain of the kinase suggests that hsp90 is likely to interact with the catalytic domain of HER-kinases. As HER-kinase heterodimers are quite sensitive to GM, we speculated that each element of the heterodimer interacts with hsp90. Accordingly, it is believed that the dimers of the invention interact with both subunits of the HER-kinase heterodimers and thus more effectively and specifically target the active form of the HER-kinase. The mechanism of action appears to be

Q4 based on degradation of the HER-kinases, but may include or in some cases be derived entirely from an inhibition of activity of the HER-kinases.

Fig. 2 shows various compounds which have been synthesized and tested for activity and selectivity as promoters of tyrosine kinase degradation. The compounds tested included geldanamycin, geldanamycin homodimers with linkers of varying lengths, species with quinone or ring-opened geldanamycin linked to geldanamycin and geldanamycin coupled to a linker with no substituent at the other end. The linker in each case is bonded to carbon-17 of the geldanamycin moiety or moieties. The crystal structure of GM bound to hsp90 shows that carbon-17 is the only one not buried in the binding pocket. Stebbins, et al., *Cell* 89, 239-250 (1997).

✓ Page 7, please replace the paragraph starting on line 23 with the following:

Q5 GMD-4c was also a potent inhibitor of the growth of breast cancer cells containing HER-kinases (Table 1) with an IC50 of 100 nM against MCF-7 compared to IC50 25 nM for GM and 650 nM for the one-ring opened dimer GMD-a. SKBR3 in which HER2 is highly overexpressed was also found to be very sensitive to GMD-4c. Most epithelial cancer cell lines express one or more members of the HER-kinase family. In order to assess whether the effects of GMD-4c on cells were specific, we utilized the 32D hematopoietic cell line. None of the members of the HER-kinase family are expressed in this murine IL3-dependent myeloid progenitor cell line. Wang, et al., *Proc Natl Acad Sci (USA)* 95, 6809-6814 (1998). GM is a potent inhibitor of 32D; GMD-4c does not appreciably affect its growth.

✓ On Page 8, please replace the first paragraph with the following:

Q6 Based on these experimental results, we conclude that GMD-4c induces the selective degradation and/or inhibition of HER-family kinases and specifically inhibits the growth of HER-kinase containing tumor cell lines. This work supports the idea that selective ansamycins with a different, more restricted spectrum of targets than the parent molecules can be synthesized. In this case, the mechanism of selectivity is not yet known, but depends on the

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a⁶ presence of both GM moieties and is a function of the length of the linker. GMD-4c may selectively interact with HER-kinase heterodimers, but it is also possible that it preferentially interacts with different hsp90 family members than GM.

/ On Page 9 of the specification, please replace the partial paragraph starting on line 1 as follows:

a⁷ 100% dimethylsulfoxide (DMSO) and stored at -20°C prior to use in preparation of the geldanamycin derivatives of Fig. 2. The GM analogs were prepared according to the procedure depicted in Fig. 1, which is modified from the method of Schnur et al., *J. Med. Chem.* 38, 3813-3820 (1995). Briefly, the geldanamycin dimers (GMDs) were prepared by treatment of GM with 0.5 eq. of the appropriate diamine in DMSO. The ansa ring-opened GMDs (GMD-a and GMD-aa) were prepared by methanolysis (NaOMe/MeOH) of the GMD-4c. GM-quinone was synthesized by first treating GM with excess 1,4-diamobutane, then addition of 2-methoxy-1-hydroxymethylquinone.

TOT260" 26TZE660
In the Figures:

Please replace figures 1 and 2 with the enclosed replacement sheets.

In the claims:

Please cancel claims 1, 2, 5 and 8 without prejudice and amend claims 3, 9, 12 and 13 to read as follows:

a⁸ 3. (amended) A chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

a⁹ 6. (amended) The chemical compound of claim 4, wherein the linker has a length of 4 to 7 carbon atoms.